THYROID PROFILE IN ABNORMAL UTERINE BLEEDING

Dissertation submitted to

THE TAMILNADU DR. M.G.R MEDICAL UNIVERSITY, CHENNAI

With fulfillment of the regulations

For the award of the Degree of

M.D (Obstetrics and Gynaecology)

Branch – II

GOVERNMENT STANLEY MEDICAL COLLEGE

CHENNAI

MARCH 2010

CERTIFICATE

This is to certify that this dissertation entitled **"THYROID PROFILE IN ABNORMAL UTERINE BLEEDING"** submitted by **DR.JAYALAKSHMI.G.SHENOY** appearing for part II M.D. branch II Obstetrics and Gynaecology degree examination in March 2010, is a bonafide record of work done by her under my direct guidance and supervision as per the rules and regulations of the Tamil Nadu Dr. M.G.R. Medical University Chennai, Tamil Nadu. I forward this to The Tamil Nadu Dr. M.G.R Medical University, Chennai, Tamil Nadu, India.

Professor and Head
Department of Obstetric and Gynaecology
Stanley Medical College
Chennai -600 001

THE DEAN

Stanley Medical College
Chennai - 600 001

ACKNOWLEDGEMENT

I am greatly indebted to **Dr. A.PRIYA M.S., D.O.,** Dean, Stanley Medical College and Hospital, Chennai for permitting me to utilize the hospital facilities for conducting this study.

I am extremely grateful to **Dr. C.VENI M.D., D.G.O., Dip.N.B.,** professor, HOD and superintendent, Govt, RSRM Lying in Hospital, Chennai for all her support.

I express my deep gratitude to Prof. **Dr. A.P. NALINI M.D. D.G.O.,** Govt, RSRM Lying in Hospital, Stanley Medical College who suggested this topic to me and for her valuable guidance throughout my study.

I am thankful to **Prof. Dr. A. KALAICHELVI, M.D. D.G.O., Dip.N.B., Prof. Dr. T. RUCKMANI M.D. D.G.O., Prof. Dr. HEPHZIBAH KIRUBAMANI M.D. D.G.O., Ph.D.,** for their invaluable help in every step during this study.

I will be failing in my duty if I do not express my sincere thanks to all the patients for the consent and cooperation they extended for this study.

CONTENTS

INTRODUCTION

Thyroid dysfunction is a common cause of AUB and accounts for 25-35% of cases (Koutras DA, 1997). Thyroid disorders are 10 times more common in women than men (Sisan et al, 1987). Approximately 1% of the female population will develop overt hypothyroidism (Turnbridge WMG, 1977,)

Abnormal menstrual cycles are occasionally the first sign of hypothyroidism and hyperthyroidism. (Wilansky DL, Griesman B, 1992)

The clinical objective is to detect and treat thyroid disease before the symptoms and signs are significant and intense. Therefore the key to early diagnosis is to maintain a high index of suspicion and to readily screen for the presence of abnormal thyroid function. Moreover, thyroid dysfunction is an easily correctable cause of AUB. Appropriate treatment is rewarded by the prompt return of normal menstrual cycles.

AIM OF THE STUDY

The study is aimed at a cross- section of population presenting to the department of Obstetrics and Gynecology at the Government RSRM Lying- in Hospital, Stanley Medical College with complaints of abnormal uterine bleeding. The study aims to ascertain the following.

1) The association between thyroid dysfunction and AUB in the reproductive age group (18-45 years).
2) To study the thyroid abnormalities in different types of AUB in the reproductive age group.
3) To establish if screening for thyroid abnormalities is justified using T3 , T_4 and TSH.

REVIEW OF LITERATURE

1. Gardner and Hill in 1927 showed an association between hypothyroidism and menorrhagia
2. Goldsmith et al in 1952 found that 8 out of 10 patients with hypothyroidism had anovulation with only 2 experiencing normal ovulation and menses.
3. Rogers et al 1958 stated that the most common abnormality observed by hypothyroid women is a change in the character of uterine bleeding and length of the cycle.
4. Scott in 1964 found that 56% of woman with hypothyroidism had abnormal menstrual patterns with menorrhagia being the most common.
5. Blum and Blum in 1972 have studied the relationship between subclinical hypothyroidism and menorrhagia.
6. Geenspan et al in 1975 advocated the empirical use of the thyroxine. But in 1999, prentice et al have stated that the empirical use of thyroxine is controversial. They have condemned it and advocated the use of TRH in women with AUB and normal T_3, T_4, and TSH.
7. Akande in 1975 stated that changes in FSH/LH ratios caused anovulatory cycles in hypothyroidism.
8. Andrew weeks in 1987 in his study of 650 women with menstrual disturbances at the Jessop hospital has stated that hypothyroidism is a greatly under diagnosed causes of menorrhagia.

9. Keye WR, Yuen B Knopff in 1976 have stated that hyperprolactinemia causing luteal phase defect is associated with less severe forms of hypothyroidism
10. Robuschi et al in 1987 have stated that hypothyroidism increases with age and is more common in older women. Upto 45% of thyroid glands from women over 60 show evidence of thyroiditis. The incidence of anti-thyroglobulin antibodies is 7.4% in women over age 75 while 16.9% of woman aged 60 and 17.4% of woman over age 75 have elevated TSH levels. In women admitted to geriatric wards, 2-4% have clinically apparent hypothyroidism
11. Klee et al in 1987 have shown the significance and positive predictive value of TSH assay in thyroid functions tests. They are of opinion that TSH based testing strategies minimize the problems of abnormal T_4 study and significantly reduce the number of TRH stimulation tests performed.
12. Smith et al in 1987 showed an association between hypothyroidism and menorrhagia with development of an advanced form of von willebrand's disease in untreated hypothyroidism . The hemostatic defects returned to normal with thyroxine supplementation.
13. Bleney et al in 1990 confirmed the findings of Smith et al. Hingham in 1992 reported a case of hypothyroidism in which menstrual loss was

measured. An initial loss of 480 ml decreased to 58 ml following a 3 months treatment with thyroxine.

14. wilansky et al in 1992 performed thyrotropin releasing hormone (TRH) test in 67 women who complained of excessive menstrual loss. All had normal levels of thyroxine and thyroid stimulating hormone (TSH). They found that 22% had abnormal TRH tests and they treated these women with thyroxine. At follow up between 12 and 36 months later, all considered their menstrual loss to be normal. In the 16 women with normal TRH tests, 56% still complained of menorrhagia.
15. Blum and Blum in 1992 studied the possible relationship between menorrhagia and occult hypothyroidism in IUD- wearing women. They studied 40 women with menorrhagia secondary to an intrauterine contraceptive device. They all had normal free thyroxine and TSH levels. The 10 patients who had the highest TSH levels were given a TRH test and all proved to have early hypothyroidism. All patients reported a significant improvement with thyroxine treatment. This recent development deserves further study.
16. Danese MD et al in 1996 have stated that hypothyroidism is frequent enough to warrant consideration in most older women. They recommend screening with highly sensitive TSH assay every 5 years beginning at age 35 and then every two years beginning at age 60 or with the appearance of any symptom suggesting hypothyroidism

17. Chameron and Fraser in 1998 in their study on the clinical disorders of the endometrium and the menstrual cycle have stated that thyroid disorders are the most common endocrine abnormality associated with menstrual disturbances. Hypothyroidism is a potent cause of menorrhagia which is amenable to treatment.
18. Shaw RW in 1999 conducted a large comparative analysis to study the effect of thyroxine replacement on menstrual blood loss in hypothyroid patients. There was a relative improvement in hemoglobin concentration and general condition of the patients.
19. Prentice et al – Medical Management of Menorrhagia – 1999 have stated that all women with unexplained menorrhagia should be tested for thyroid dysfunction.

The review of literature suggests that there is a strong correlation between AUB and thyroid dysfunction. It stands as an easily correctable cause of AUB.

PHYSIOLOGY OF MENSTRUATION

Menstruation is a very recent phenomenon in the evolutionary time line. It occurs in very few species even among viviparous animals.The diagnosis and management of abnormal menstrual function must be based on an understanding of the physiologic mechanisms involved in the regulation of the normal cycles. Although the activity of the endometrium is directly controlled by the ovarian function and by the two hormones secreted by the ovary, the ovary itself is activated by the pituitary gland, the secretion of which is under the nervous control of the hypothalamus.

The normal human menstrual cycle can be divided into two segments: the ovarian cycle and the uterine cycles based on the organ under examination. The ovarian cycle may be further divided into follicular and luteal phases, whereas the uterine cycle is divided into the corresponding proliferative and secretory phases.

(1) At the beginning of each monthly menstrual cycle, levels of gonadal steroids are low and have been decreasing since the end of the luteal phase of the previous cycle.

(2) With the demise of the corpus luteum, FSH levels begin to rise and a cohort of growing follicles is recruited. These follicles each secrete increasing levels of oestrogen as they grow in the follicular phase. This in turn, is the stimulus for uterine endometrial proliferation.

(3) Rising oestrogen levels provide a negative feed back on pituitary FSH secretion which begins to wane by the midpoint of the follicular phase. Conversely, LH initially decreases in response to rising estradiol levels but late in the follicular phase the LH level is increased dramatically (biphasic response).

(4) At the end of the follicular phase (just prior to ovulation), FSH induced LH receptors are present on granulosa cells and with LH stimulation, modulate the release of Progesterone.

(5) After a sufficient degree of oestrogenic stimulation, the pituitary LH surge is triggered, which is the proximate cause of ovulation which occurs 24-36 hours latter. Ovulation heralds the transition to luteal secretory phase.

(6) The oestrogen level decreases through the early luteal phase from just before ovulation until the midluteal phase when it begins to rise again as a result of corpus luteum secretion.

(7) Progesterone levels rise precipitously after ovulation and can be used as a presumptive sign that ovulation has occurred.

(8) Both oestrogen and progesterone levels remain elevated throughout the life of the corpus luteum and then wane with its demise, thereby setting the stage for the next cycle.

(9) In the absence of implantation, glandular secretion ceases and an irregular breakdown of the decidua functionalis occurs. The result is a shedding of this layer of the endometrium , a process termed menses.

THE NORMAL MENSTRUAL CYCLE

A normal menstrual cycle lasts from 21 to 35 days with 2 to 6 days of flow and an average blood loss of 20-60ml. (Vollman RF, 1977 and Treloar AE, 1967). However studies of large numbers of women with normal menstrual cycles have shown that only approximately two- thirds of adult women have cycles lasting 21-35 days (Friedman E, 1977). The extremes of reproductive life are characterized by a higher percentage of anovulatory or irregularly timed cycles (Collett ME et al, 1954).

DEFINITION OF MENSTRUAL CYCLE IRREGULARITIES

(1) oligomenorrhea	:	Infrequent, irregularly timed episodes Of bleeding usually occurring at interval of more than 35 days
(2) Polymenorrhea	:	Frequent but regularly timed episodes of bleeding usually occurring at interval of 21 days or less.
(3) Menorrhagia	:	Regularly timed episodes of bleeding That are excessive in amount (>80 ml) or duration of flow (>5days).

(4) Metrorrhagia	:	Inter menstrual bleeding
(5) Menometrorrhagia	:	Excessive, prolonged bleeding that Occurs at irregularly timed, frequent Intervals
(6) Hypomenorrhea	:	Regularly timed bleeding that is decreased in amount.
(7) Amenorrhea	:	Absence of menstruation for three Normal cycles or six moths.

THE THYROID GLAND

Thomas Wharton in 1656, gave the thyroid gland its modern name. For unknown reasons, thyroid disease is more common in women than in men (Medvei VC, 1993)

Normal thyroid Physiology

Thyroid hormone synthesis depends on an adequate supply of iodine in the diet. It is absorbed as iodide and enters the thyroid under the influence of TSH. Within the gland iodide is oxidized to elemental iodine which is then bound to tyrosine. Mono and di-iodotyrosines combine to form thyroxine (T_4) and triiodothyronine(T_3) (Norman AW, Litwack G, 1987). These compounds are part of the thyroglobulin molecule which serves as a storage depot for the thyroid hormone. TSH induces a proteolytic enzyme that result in the release of iodothyronines into the bloodstream as thyroid hormone. Removal of one iodine from the phenolic ring of T_4 yields T_3

One – third of T_4 Secreted each day is converted in the peripheral tissues, largely in the liver and kidney to T3 and about 40% is converted into inactive Reverse T_3. Although T_4 in secreted at 20 times the rate of T_3 ,T_3 is responsible for most of the thyroid action in the body (Czarnocka B et al, 1985).

Mechanism of Thyroid Hormone Action

Thyroid hormone acts by binding to a specific nuclear DNA bound thyroid hormone receptor (TR) usually as a hetero dimer with the retinoid X receptor (RXR) at specific sequences dictated by the DNA binding site preferences of

the RXR-TR complex. T_3 has a 15 fold higher binding affinity for TR than does T_4 which explains its function as the active thyroid hormone (Brent GA, 1994)

Bound and free fractions of Thyroid Hormones

Thyroid hormones present in circulation are mainly bound to proteins. Approximately 70% of thyroid hormones are bound to thyroxine binding globulin (TBG).The remaining 30% is bound to thyroxin binding prealbumin and albumin. The binding proteins have greater affinity for T_4 and thus allow T_3 to have a greater entry into the cells. TBG is synthesized in the liver and the synthesized in the liver and the synthesis is increased by oestrogens.

Regulation of thyroid hormone secretion – Role of estrogens

Thyroid hormones regulate TSH secretion by suppressing TRH secretion, but primarily affect the pituitary sensitivity to TRH, by reducing the number of TRH receptors. Pituitary secretion of TSH is very sensitive to changes in the circulating level of thyroid hormone. A slight change in the circulating level of T_4 will produce a many fold greater response in TSH. TSH secreting cells are regulated by T_4 but only after the T_4 is converted to T_3 in the pituitary cells. Although some tissues depend mainly on the blood T_3 for their intracellular T_3, the brain and pituitary depend on their own intracellular conversion of T_4

The measurement of T3,T4 and TSH therefore provides the most accurate assessment of thyroid function.

The TSH response to TRH is influenced mainly by the thyroid hormone concentration in the circulation. Estrogen increases the TRH receptor content in the pituitary. Hence the TSH response to TRH is greater in women than in men and greater in women taking oral contraceptives.

The smallest doses of the TRH that are capable of producing an increase in TSH also increase the prolactin levels indicating a physiologic role for TRH in the control of prolactin secretion.

Thyroid Function Tests

Serum thyroid hormones are measured by radio- immunoassay. Conditions that elevate the TBG (pregnancy, oestrogen replacement, use of oral contraceptive pills, hepatitis) necessitate measurement of T_3 resin uptake for clarification

(1) Free Thyroxine (FT_4): Assays that measure free T_4 are usually displacement assays using an autoantibody to T_4. The result is not affected by changes in TBG and binding.

(2) Total thyroxine (T T_4): The total thyroxine, both the portion bound to TBG and the free unbound portion is measured by displacement assays and in the absence of hormone therapy and other illnesses estimates the thyroxine concentration in the blood.

(3) TSH: TSH is measured by highly sensitive assays that can detect concentrations as low as 0.01μu/L. This is a very sensitive indicator of thyroid hormone action at tissue level because it is dependent on the pituitary exposure to T_4 . In the absence of hypothalamic or pituitary

disease, the sensitive TSH assays will provide the best indication of excess or deficient thyroxine, slight changes in T_4 are reflected in a many fold greater response in TSH. Transient changes in TSH are seen in severe systemic illness, psychiatric illness, adrenal insufficiency, corticosteroid therapy, elevated HCG (Since HCG can stimulate the TSH receptor) and in any acute illness.

(4) Total T_3 and Reverse T_3: These are rarely required for the accurate evaluation of a patient with an abnormal TSH level and are of little value in clinical circumstances. Serum T_3 is almost always an indirect reflection of the serum T_4 supply (Berghout A, 1994)

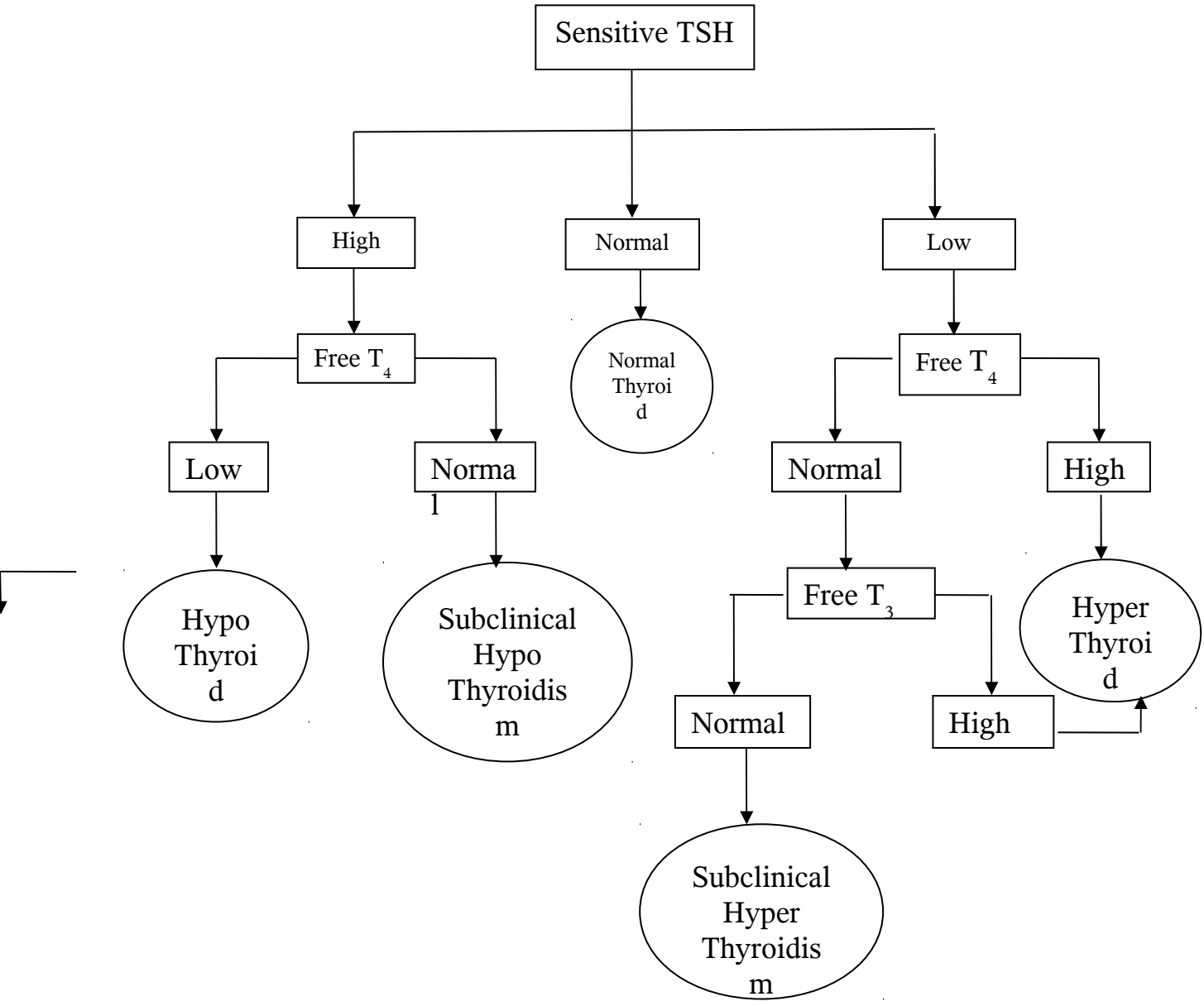
Other tests include the free thyroxine index and radioactive iodine uptake.

THE LABORATORY EVALUATION

For screening purposes or when there is a relatively low clinical suspicion of thyroid disease, the initial step is to measure the TSH by a sensitive assay. A normal TSH essential excludes hypo/ Hyperthyroidism. A high TSH requires the measurement of free T_4 to confirm the diagnosis of hypothyroidism. If the initial TSH is low, especially less than 0.08 μu/ml, then measurement of high T4 will confirm the diagnosis of hyperthyroidism. If T4 is normal, the T_3 level is measured since some patients will have predominately T_3 toxicosis,

If T_3 is normal it implies that thyroxine secretion is autonomous from TSH and this is called subclinical hyperthyroidism. Some of these patients will eventually have increased T_4 or T_3 levels with true hyperthyroidism.

The algorithm represents a cost-effective and accurate clinical strategy.



(Surks MI, chopra H, Mariesh CN, Nicoloff JT, solomon, TH American Thyroid Association guidelines for use of laboratory tests in thyroid disorders, JAMA 263:1529, 1990)

Role of Thyroid in Reproductive physiology/ Pathology

The following facts emphasis the role of thyroid hormone in the female reproductive physiology.

(1) TSH receptors have been found on granulosa cells.

(2) T_3 and T_4 have been found in follicular fluids.

(3) T_4 has been found to enhance the action of gonadotrophins in luteinisation and progesterone secretion

The female hormonal milieu and its potential effects on immune surveillance undoubtedly play a role in the increased risk (10 fold) of women to develop autoimmune thyroid disease (Gaitan E et al, 1985 and Wenzel BE et al, 1987). The immunoglobulins produced against the thyroid are polyclonal and the multiple combinations of various antibodies present combine to create the clinical spectrum of autoimmune thyroid diseases that affect successful reproductive function.

Foetal and neonatal period.

Very few data exist regarding the role of the thyroid hormones in the reproductive system of the foetus. No effective human studies are available. Thyroid excess in mice is shown to cause early maturation of the reproductive tract and early opening of the vagina. Hypothyroidism in mice causes small ovaries deficient in cholesterol. No change has been observed in human fetuses.

Hypothyroidism

(i) **Prepubertal /Pubertal**

In both sexes, thyroid hormones influence sexual development and reproductive function.

Infantile hypothyroidism, if untreated, leads to sexual immaturity. Juvenile hypothyroidism causes a delay in the onset of puberty followed by anovulatory cycles.

Paradoxically, primary hypothyroidism may also cause precocious sexual development and galactorrhea. (Kleinberg DL, New England J.Med. 1977). The McCune Albright syndrome is characterized by hyperfunctioning endocrinopathies including hyper/hypothyroidism and sexual precocity, but the association may be coincidental (Albright F, Maine MJ, 1938). Precocious puberty with delayed bone age suggests primary hypothyroidism. Serum TSH is increased, T4 is low and galactorrhea may be present with increased serum prolactin (Honbo KS et al, 1978). (Kindle et al) have described a syndrome of precocious menstruation, galactorrhea and sella enlargement in girls with juvenile hypothyroidism.

2. **In adult women**

Severe hypothyroidism is associated with diminished libido, amenorrhea or anovualtion (Grodstein F et al, 1993). Secretion of progesterone is inadequate and endometrial proliferation persists resulting in excessive and irregular breakthrough menstrual bleeding. These changes may be due to

deficient secretion of luteinizing hormone. Rarely in primary hypothyroidism, secondary depression of pituitary function may lead to ovarian atrophy and amenorrhea. Hypothyroidism appears to be associated with decreased fertility resulting form ovulatory difficulties, and spontaneous abortions may result, although many pregnancies are successful. (Lao TTH et al, 1988 and Morimotoc et al, 1990)

The values for plasma gonadotrophins are usually in the normal range in primary hypothyroidism. In postmenopausal women, levels are usually lower than euthyroid women of the same age but are nevertheless within the menopausal range. This provides a valuable means of differentiating primary from secondary hypothyroidism.(Melmed S,Hershman J,1982)

Myxedematous infiltration can produce enlarged , cystic ovaries (Kansen KA et al, 1997)

There may be a high incidence of early or potential hypothyroidism in women presenting with menorrhagia. Hypothyroidism can cause menorrhagia/ polymenoorrhea.-these symptoms being present in 30-40% of the cases. (Koutras DA, 1997)

Metabolism of oestrogens in hypothyroidism

The metabolism of oestrogens is also altered. With respect to oestradiol and oestrone, hypothyroidism favours the metabolism of these steroids via 16 α – hydroxylation over that via 2 –oxygenation with the result that the formation of oestriol is increased and that of 2-hydroxyoestrone and its derivative 2-

methoxyoestrone is decreased. The sex hormone binding globulin (SHBG) concentrations in plasma is decreased with the result that the plasma concentrations of both testosterone and oestradiol are decreased, but the unbound fractions are increased. The alterations in steroid metabolism are corrected by restoration of the euthyroid state (Brenta GA,et al, variation of SHBG in thyroid dysfunction, 1999).

Effects of hypothyroidsm on the GnRH pulsatality.

TSH is secreted by the pituitary and its excess production causes menstrual abnormality due to its adverse effects on the GnRH pulse generator and not by directly affecting the ovary. When there is decrease in GnRH pulsatality, anovulation can occur. Even slight changes in pulsatality may result in luteal phase defect (Del pozo, 1979 and warfel W, 1992).

Primary hypothyrodism and hyperprolactinemia

Hyperprolactinemia and anovulation may be associated with primary hypothyroidism Remarkable enlargement of the pituitary with thyrotroph hyperplasia and hyperprolactinemia is frequently seen in long standing primary hypothyroidism (Franks et al, 1975)

A number of mechanisms may be involved.

1) The clearance of prolactin tends to be decreased in hypothyroidism (Warfel W, 1992)

2) Patients with severe hypothyroidism may have elevated total and free estradiol levels giving rise to increased prolactin production stimulated by excess free oestrogen (Tolis G et al, 1979).
3) The third and the most significant mechanism involves the inhibitory effects of T_3 on TRH production and on TRH receptor expression. A decrease in the T3 feedback in hypothyroidism may induce and increase in the hypothalamic TRH production and in the number of TRH receptor in the lactotroph. Increased TRH action on the lactotroph in turn may stimulate prolactin secretion (Collu R, 1986.)

The duration of hypothyroidism in important with regard to the mechanism of amenorrhea- the longer the duration, the higher the incidence of amenorrhea and higher the prolactin levels. This may be associated with decreasing hypothalamic content of dopamine with ongoing hypothyroidism. This would lead to an unopposed TRH stimulatory effect on the pituitary cells that secrete prolactin. Constant stimulation by the hypothalamic releasing hormones can result in hypertrophy or hyperplasia of the pituitary (Keye WR, 1976).

Subclinical Hypothyroidism

This term designates a situation in which an asymptomatic patient has a low normal FT_4I (Free thyroxine index) but a slightly elevated serum TSH level. The TSH elevation in these patients is modest with values typically between 5 and 15mu/L. It occurs in 5-10% of women.

Effects of Hyperthyroidism on Reproductive Function

The two primary causes of hyperthyroidism are Grave's disease (toxic diffuse goiter) and plummer's disease (toxic nodular goiter) (Lazarus JH in Lancet 349,1997). Thyrotoxicosis in early life may cause delayed sexual maturation although physical development is normal and skeletal growth maybe accelerated .Menstrual changes associated with hyperthyroidism are unpredictable, ranging from amenorrhea to oligomenorrhea and normal cycles. The intermenstrual interval may be prolonged or shortened, menstrual flow is initially diminished and ultimately ceases (McKenzie JM, 1979). Fertility maybe reduced and the risk of miscarriage is increased. In some patients menstrual cycles are predominantly anovulatory with oligomenorrhea. In most patients, however, ovulation occurs as is indicated by the secretory endometrium (Reid Rl, 1987). Hyperthyroidism seldom causes amenorrhea unless exophthalmos is present.

The mechanisms involved may be the following:

(i) Increased SHBG levels decrease the clearance of testosterone and estradiol. Increased peripheral aromatisation of androgens gives rise to oestrogens due to the increase in peripheral blood flow (Thomas R, 1987)

(ii) Another more likely mechanism is the disruption in the amplitude and frequency of LH /FSH pulses due to thyroid hormone influences on GnRH signaling (DeGroot N, 1979),

Subclincal Hyperthyroidism

The presence of a chronically suppressed serum TSH level with peripheral free thyroid hormones in the normal range is called subclinical hyperthyroidism. The incidence is 0.9%.progression to overt hyperthyroidism is uncommon. The incidence increases in older women (Felicetta JU, 1987)

Screening for primary hypothyroidism

Only a few patients with amenorrhea/ galactorrhea will have hypothyroidism that is not clinically apparent. Although it seems extravagant to measure the TSH in such a large number of patients for such a small return, because the treatment of hypothyroidism is so simple and is rewarded by a prompt return of menstrual cycles,TSH measurement is warranted (Caldwell G, 1985).

The high incidence of hypothyroidism in women, particularly if the 7-10% prevalence of subclinical hypothyroidism is included raises the issue of whether the cost of systematic periodic screening of an asymptomatic population is justified (Westman AP, BMJ, 1997). The conclusions depend to a great extent on the assumptions regarding the effectiveness and economic value of therapy in asymptomatic patients with TSH

elevation alone. An assessment of TSH levels at 5 years intervals in older women (greater than 50 years) seems justified, but further analysis of more extensive screening programs are in order (P.Reid Larsen and Terry F. Davies, 2003).

Prediction of disease onset

Patients with increased TSH and normal T_4 levels progress to overt thyroid failure at a rate of about 5% per year if thyroid auto antibody levels are elevated. If the serum TSH alone is elevated without positive thyroid antibody titres, the annual risk for hypothyroidism drops to approximately 3% per year. Most clinicians therefore treat women who have elevated serum TSH concentrations and positive thyroid antibody tests even in the absence of symptoms. (Vanderpump MPJ, Turnbridge WMG, 1996)

Thyroid dysfunction and menstrual disturbances in specific conditions

1) Anorexia nervosa

The various problems associated with anorexia represent a dysfunction of the body mechanisms regulated by the hypothalamus. Anorexics are usually amenorrhic. Many symptoms can be explained by the state of relative hypothyroidism. There appears to be a compensation for the state of malnourishment with diversion from the formation of active T_3 to the

inactive metabolite reverse T_3 -a state of chemical hypothyroidism (Herzog DB Copeland PM, 1985)

Exercise and stress induced amenorrhea.

2) In patients with exercise induced amenorrhea, there is decrease in the frequency of GnRH pulses which is assessed by measuring a decrease in the frequency of LH pulses (Olson BR, 1989). Athelets have relatively low T_4 levels but amenorrhic atheletes have an overall suppression of all circulating thyroid hormones including reverse T_3. These patients are usually hypoestrogenic, but less severe alterations may cause minimal menstrual dysfunction (Anovualtion /luteal phase defect) (Gennazani AR et al, 1991)

3) **Turners syndrome**

Patients with Turners, characterized by 45XO karyotype have a short stature, primary amenorrhea and other abnormalities. A high prevalence of autoimmune thyroid disorders is noted. Approximately 50% of adult patients with Turners have anti-thyroid peroxidase (anti-TPO) and antithyroglobulin (anti TG) antibody. Approximately 30% will develop subclinical / clinical hypothyroidism (Barbesino G et al, 1998).

4) Postpartum thyroiditis

Transient thyrotoxicosis may develop within 3-6 months after delivery and is often followed by a period of hypothyroidism of several months duration with an eventual return to euthyroid state (Amino N, 1982). In some patients, only a

hypothyroid phase is apparent. Data suggest that 8-10% of women experience thyroiditis in the postpartum period (Hayslip et al, 1988). Pregnancy is therefore an important risk factor with transient thyroiditis developing in some patients and thyroid failure developing permanently or in the early years after pregnancy in a significant proportion.

MATERIALS AND METHODS

The present study of "thyroid profile in AUB" was conducted in Govt. R.S.R.M. Lying in hospital, attached to Govt. Stanley medical college, Chennai. This is a cross-sectional study of 250 women with AUB, based on data collected from women with AUB attending the outpatient department and in-patients during a period of 10 months from January 2009 to October 2009 at this hospital. The study group included women with the following complaints.

1. Oligomenorrhea : cycle length greater than 35 days.

2. Hypomenorrhea : Bleeding lasting less than 2 days.

3. Menorrhagia : Blood loss more than 80 ml or more.

4. Polymenorrhea : Cycle length less than 22 days.

5. Amenorrhea : Absence of menstruation for 6 months or 3 consecutive menstrual cycles.

Inclusion criteria

1. Women in the age group of 18-45 years.
2. Women with any of the menstrual disturbances mentioned above.
3. Women who do not have signs of demonstrable pelvic pathology including PID.

4. Women with increased BMI.
5. Women who are not on any hormonal preparation.
6. Women who were not using any IUCD in the past two years.
7. Women with signs and symptoms of hypo/hyperthyroidism.

Exclusion criteria

1. Teenage AUB
2. Age more than 45 years.
3. Presence of palpable pelvic pathology like fibroids, polyps or cervical growths.
4. Presence of general disorders like tuberculosis.
5. Presence of diabetes, hypertension or clotting abnormalities.
6. Patients with history of bleeding diathesis.
7. Patients on drugs like aspirin, heparin, sulpha drugs, antithyroid medication, eltroxin, glucocorticoids, and amiodarone.

Symptoms and signs of hyperthyroidism

1. Weight loss more than 10 kg in 3 months or subjective weight loss.
2. Diarrhoea
3. Heat intolerance
4. Tremors
5. Tachycardia
6. Eye changes –exoptholmos

Symptoms and signs of hypothyroidism

(i) Weight gain of more than 10 kg in 3 months or subjective weight gain

(ii) Constipation

(iii) Slow mentation/ lethargy/increased sleepiness.

(iv) Elevated cholesterol

(v) Coarse skin.

PROCEDURE

Patients were selected based on the above criteria and history was taken as per the proforma including a detailed menstrual history and questions regarding the signs and symptoms of hypothyroidism and hyperthyroidism were asked.The following examination was done.

A detailed general examination focusing specifically on the presence/ absence of anemia, thyroid swelling , cardiovascular abnormality, gross nervous system dysfunction, galactorrhea and abnormal hair distribution. The height in centimeters and weight in kilograms was measured and the BMI calculated. An abdominal, speculum examination and pelvic examination were done to rule out other causes of abnormal bleeding.5 ml of venous blood was taken in a dry plain glass container without any anticoagulant for TSH assay and T3,T_4 estimation. Morning sample in the fasting state was taken. TSH assay was performed using ultrasensitives solid

phase –two site immune radiometric assay (IRMA). IRMA- K9 kit supplied by Board of Radiation and isotope Technology (BRIT), Bombay was used. The physiological range was 0.3-6.18μIU/ml with due consideration given to diurnal /pulsatile variation.

T3 and T_4 was analysed using RIA K-5/5A kit supplied by BRIT, Bombay . The physiological range for T4 was 4.8 to 11.5μg/dl. The physiological range for T3 was 0.5 to 1.5 ng/ml.

ANALYSIS OF THE STUDY

After ruling out those patients with palpable organic pelvic pathology by gynaec examination and ultrasonogram, A total of 250 patients were included in the study group.

TABLE – 1

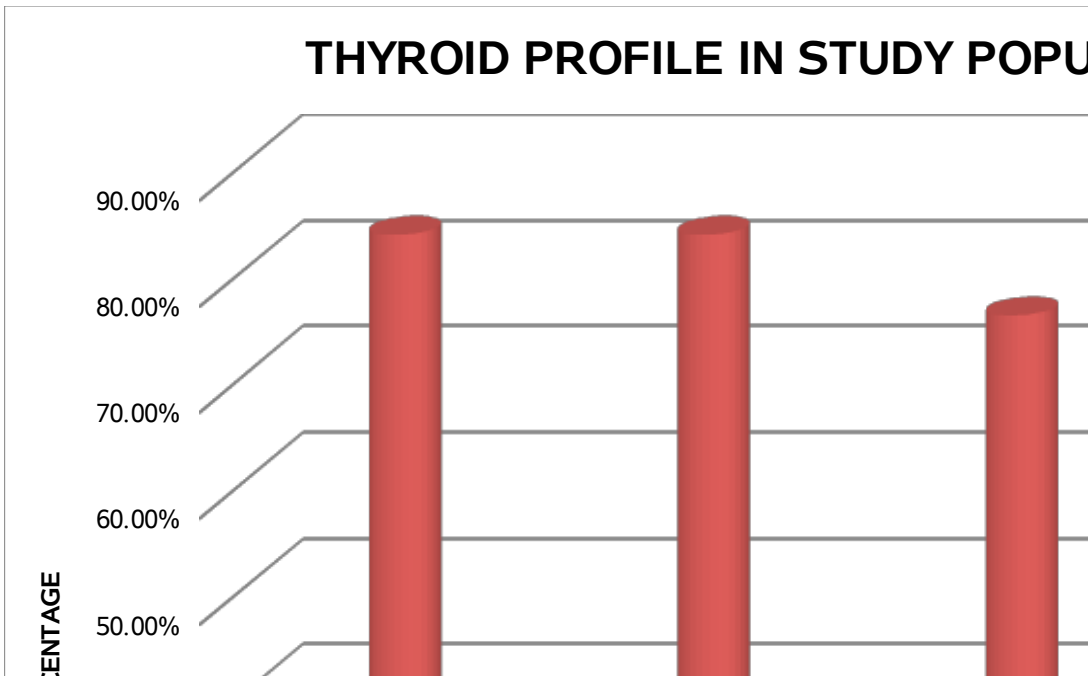
T_3 VALUES

	Frequency	**Percentage**
< 0.5 ng/ml	34	13.6%
0.5 – 1.5 ng/ ml	206	83.6%
>1.5 ng/ml	10	3.8%

TABLE – 2

T_4 VALUES (N 4.8 – 11.5 µg/dl)

T_4 (µg/dl)	**Number**	**Percentage**
< 4.8	34	13.6%
4.8 – 11.5	206	83.6%
>11.5	10	3.8%


THYROID PROFILE IN STUDY POPU
90.00%
80.00%
70.00%
60.00%
50.00%
ENTAGE

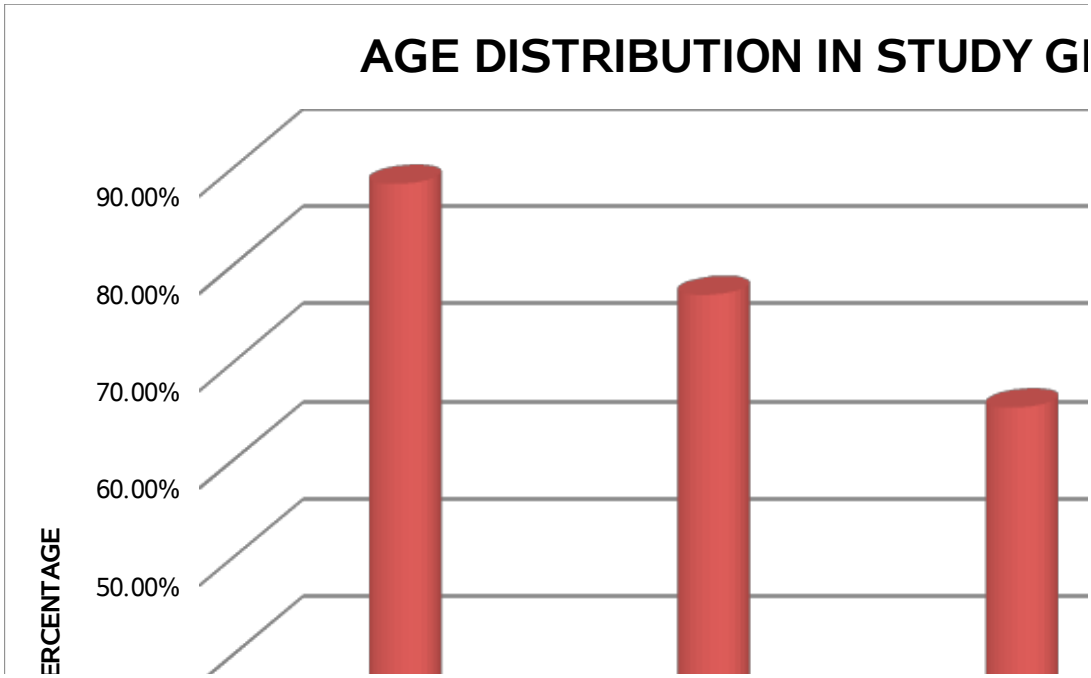

AGE DISTRIBUTION IN STUDY GI
90.00%
80.00%
70.00%
60.00%
50.00%
ERCENTAGE

TABLE – 3

TSH VALUES (N 0.3- 6.18 µIU/ml)

TSH (µIU/ml)	Number	Percentage
< 0.3	14	5.6%
0.3- 6.18	190	76%
>6.28	46	18.4%

Among 250 patients, 190 patients had normal TSH values. Incidence of Clinical hypothyroidism was 13.6%,

Incidence of subclinical hypothyroidism was 4.8%

Incidence of clinical hyperthyroidism was 4%

Incidence of subclinical hyperthyroidism was 1.6%.

TABLE -4

AGE DISTRIBUTION IN STUDY GROUP

AGE GROUP	Hypothyroidism		Euthyroidism		Hyperthyroidism	

	No.of pts.	Percentage	No.of pts.	Percentage	No.of pts.	Percentage
18-23 Yrs	2	6.06%	29	87.80%	2	6.06%
24-31 Yrs	26	18.05%	110	76.38%	8	5.55%
32-40 Yrs	16	29.62%	35	64.81%	3	5.55%
>40 Yrs	2	10.52%	16	84.21%	1	5.26%

Out of 250 patients,198 patients were in the age group of 24-40 years. Among 198 patients,42 patients were hypothyroid and 11 patients were hyperthyroid.

TABLE 5

TYPE OF AUB IN STUDY GROUP

Type of AUB	No.of patients	Percentage
Oligomenorrhea	77	30.80%
Menorrhagia	109	43.60%
Amenorrhea	49	19.60%
Hypomenorrhea	7	2.80%
Polymenorrhea	8	3.20%

Majority of patients in the study group had menorrhagia(43.60%) and oligomenorrhea(30.80%)

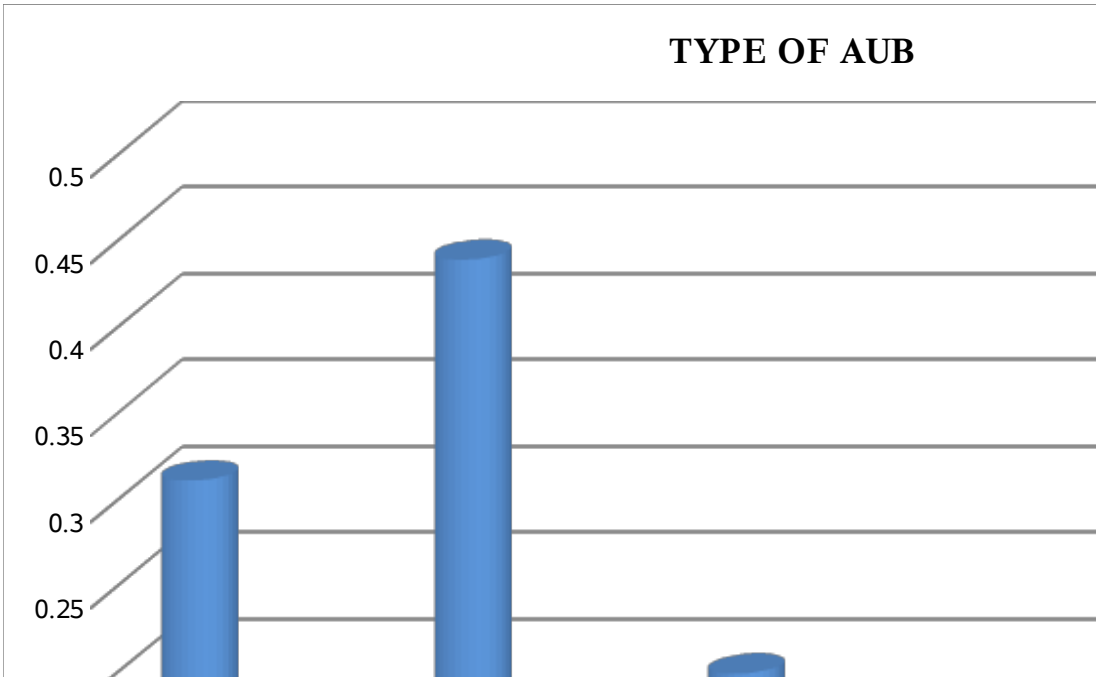


TABLE – 6

GENERAL EXAMINATION

General Examination	Number	Percentage
Normal	196	78.40%
Anaemia	45	18.0%
Thyromegaly	9	3.60%

21.6% of the patients had abnormal findings on examination. 78.4% were normal.

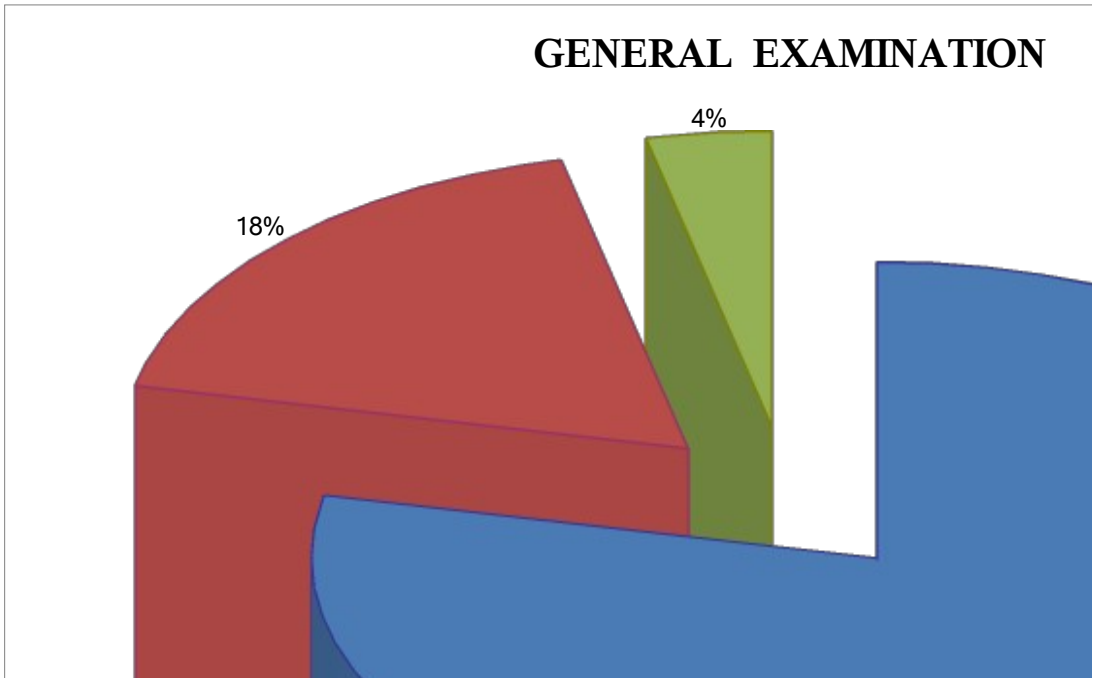


TABLE – 7
BODY MASS INDEX

BMI Range	Hypothyroidism		Euthyroidism		Hyperthyroidism	

	No.of pts.	Percentage	No.of pts.	Percentage	No.of pts.	Percentage
<18(lean)	-	-	2	16.66%	10	83.33%
18-24(Normal)	9	5.52%	150	92.02%	4	2.45%
25-29(overweight)	22	40.74%	32	59.25%	-	-
30-34(obese)	13	81.25%	3	18.75%	-	-
>35 (morbid obese)	2	40%	3	60%	-	-

Increased BMI was found in hypothyroid patients. Decreased BMI was found in hyperthyroid patients.

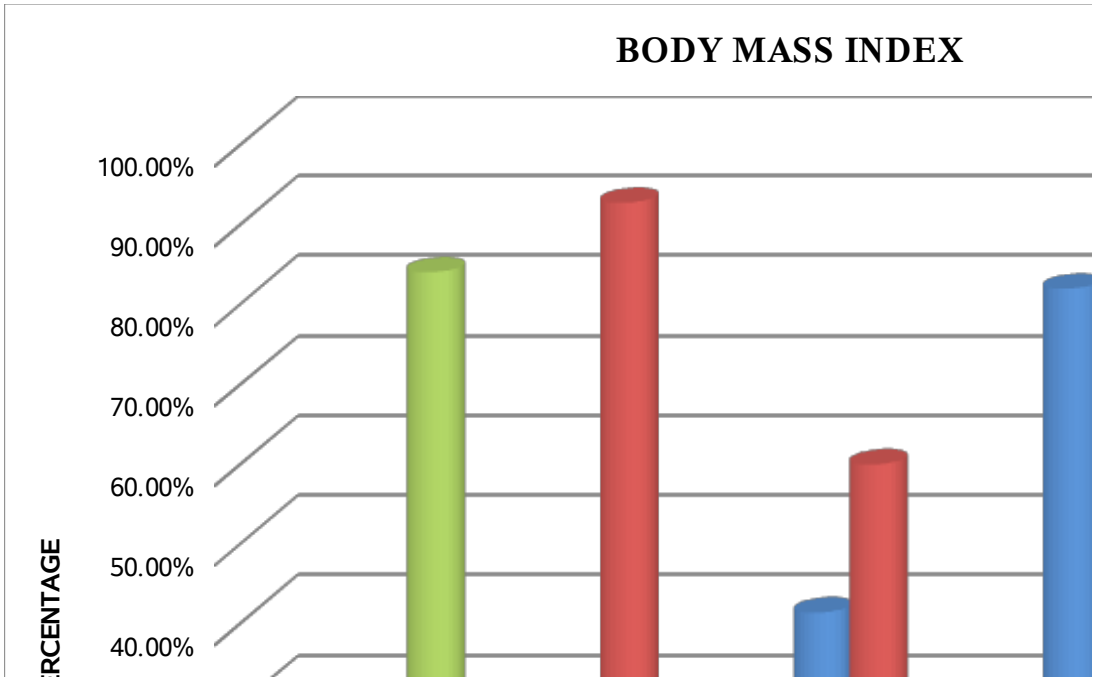


TABLE – 8

FRACTIONAL CURETTAGE

Endometrial curettage	Hypothyroidism		Euthyroidism		Hyperthyroidism	

	No.of pts.	Percentage	No.of pts.	Percentage	No.of pts.	Percentage
Secretory	6	13.0%	140	73.68%	8	57.14%
Proliferative	40	87%	50	26.32%	6	42.86%

Majority of hypothyroid patients(87%) had proliferative pattern due to anovulation. In hyperthyroid patients both proliferative and secretory pattern were seen.

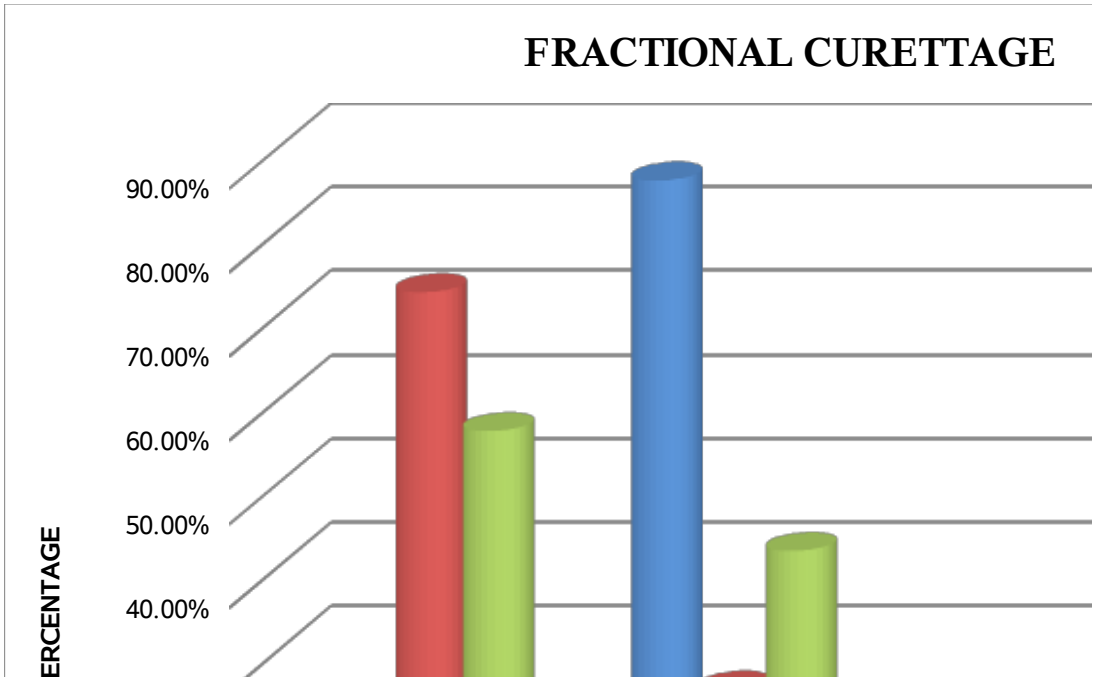


TABLE- 9

HEMOGLOBIN ESTIMATION

Hemoglobin	Hypothyroidism		Euthyroidism		Hyperthyroidism	

	No.of pts.	Percentage	No.of pts.	Percentage	No.of pts.	Percentage
<7 gms%	30	65.2%	20	10.52%	-	-
7-9 gms%	5	10.95	30	15.795	4	28.57%
>9 gms%	11	23.9%	140	73.69%	10	71.43%

Majority of hypothyroid patients(65.2%) were anemic due to menorrhagia,whereas hemoglobin was normal in majority of hyperthyroid patients(71.43%)

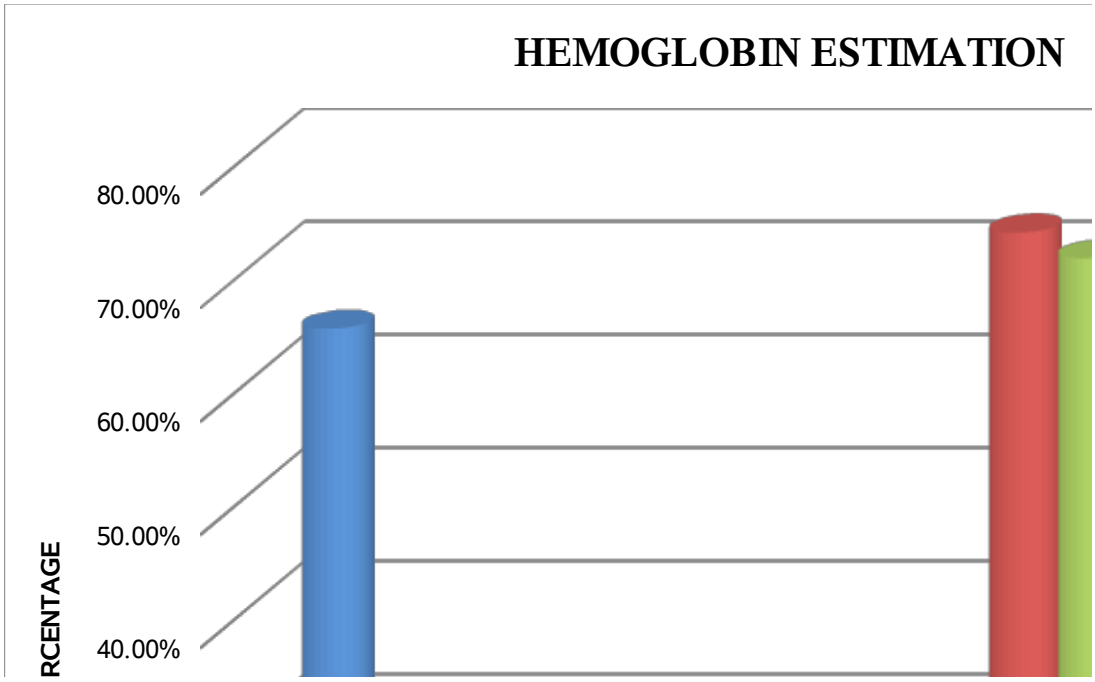


TABLE 10

SIGNS AND SYMPTOMS OF HYPOTHYROIDISM

Signs/Symptoms	Number of patients	percentage
Constipation	**10**	**29.4%**
Cold intolerance	**1**	**2.9%**
Voice change	**1**	**2.9%**
Weight gain	**20**	**58.8%**
Lethargy	**2**	**5.9%**

Among 34 hypothyroid patients,the commonest symptom was weight gain(58.8%) followed by constipation(29.4%)

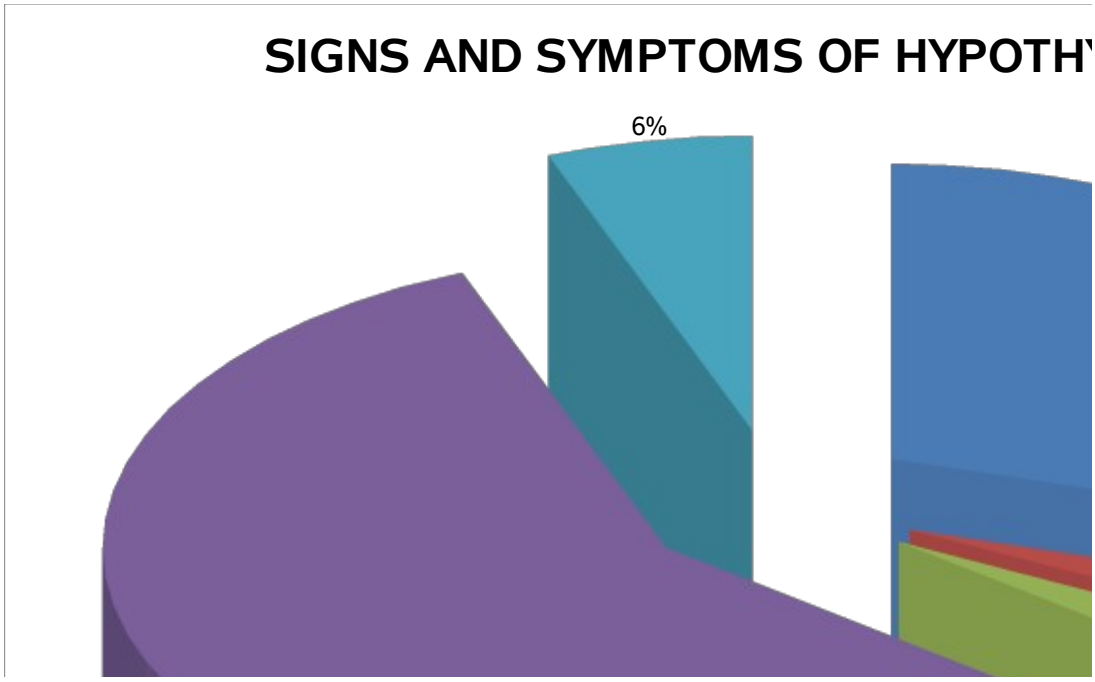


TABLE – 11

SIGNS AND SYMPTOMS OF HYPERTHYROIDISM

Signs/Symptoms	Number of patients	Percentage
Heat intolerance	**1**	**10%**
Anxiety	**1**	**10%**
Weight loss	**1**	**10%**
Fatigue	**5**	**50%**
Tremors	**1**	**10%**
Diarrhea	**1**	**10%**

Among 10 hyperthyroid patients,the commonest symptom was fatigue(50%)

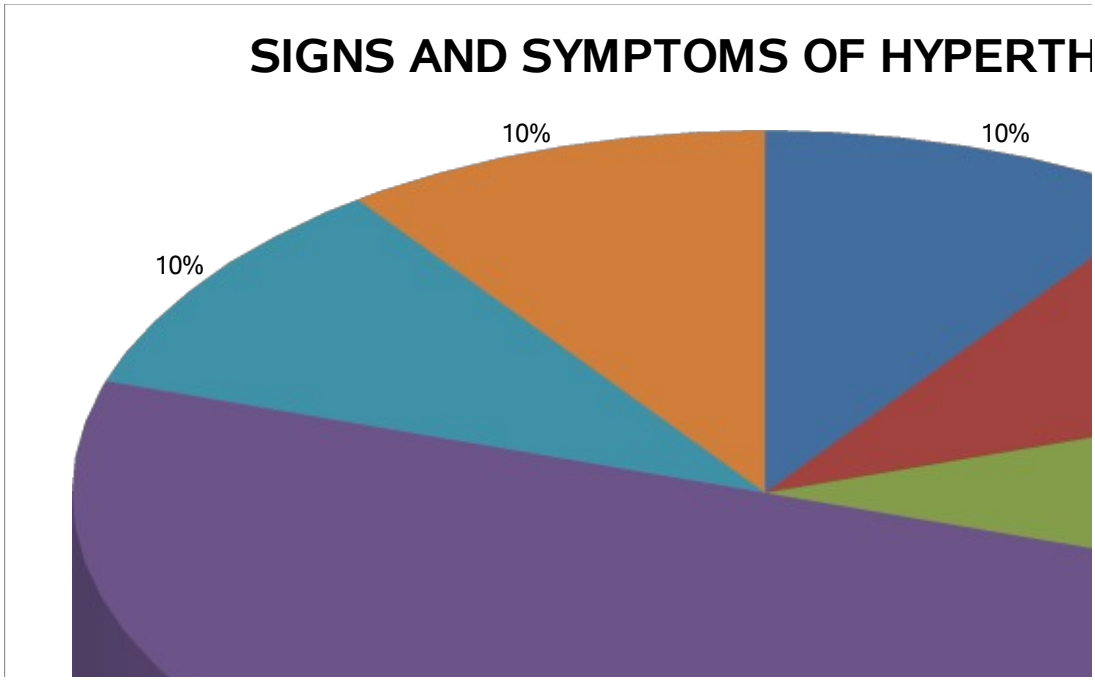


TABLE-12

AMENORRHEA-T_3,T_4 AND TSH VALUES

Values	T3 (N=0.5-1.5 ng/ml)	T4 (N=4.8-11.5µg/dl)	TSH N=0.3-6.18µIU/ml)

	No.of pts.	Percentage	No.of pts.	Percentage	No.of pts.	Percentage
< Normal	2	4.1%	2	4.08%	8	16.32%
Normal	41	83.7%	41	83.7%	38	77.56%
>Normal	6	12.3%	6	12.3%	3	6.12%

Out of 49 patients with Amenorrhea,

2 patients (0.8%*) had clinical hypothyroidism
6 patients (2.4%*) had clinical hyperthyroidism
1 patient (0.4%*) had subclinical hypothyroidism
2 patients (0.8%*) had subclinical hyperthyroidism

* → of the total sample studied

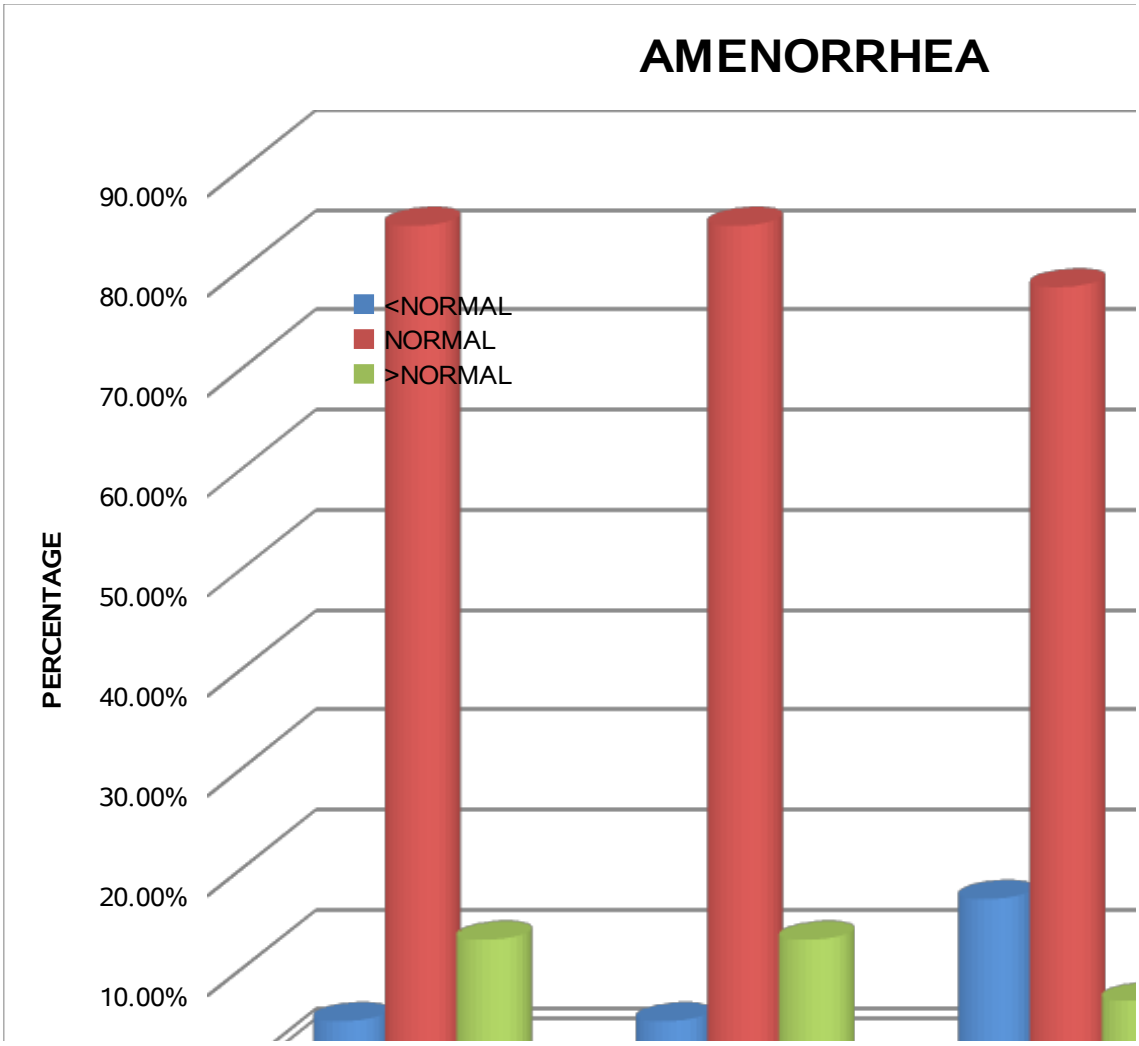

AMENORRHEA
PERCENTAGE
90.00%
80.00%
70.00%
60.00%
50.00%
40.00%
30.00%
20.00%
10.00%
<NORMAL
NORMAL
>NORMAL

TABLE-13

MENORRHAGIA-T_3,T_4 AND TSH VALUES

Values	T3 (N=0.5-1.5 ng/ml)		T4 (N=4.8-11.5µg/dl)		TSH N=0.3-6.18µIU/ml)	

	No.of pts.	Percentage	No.of pts.	Percentage	No.of pts.	Percentage
< Normal	26	23.85%	26	23.85%	1	2.03%
Normal	82	75.22%	82	75.22%	74	67.89%
>Normal	1	2.03%	1	2.03%	34	31.19%

Among 109 patients with menorrhagia,

26 patients(10.4%*) had clinical hypothyroidism
1 patient (0.4%*) had clinical hyperthyroidism
8 patients(3.2%*) had subclinical hypothyroidism
No patient had subclinical hyperthyroidism in this group.

* → of the total sample studied

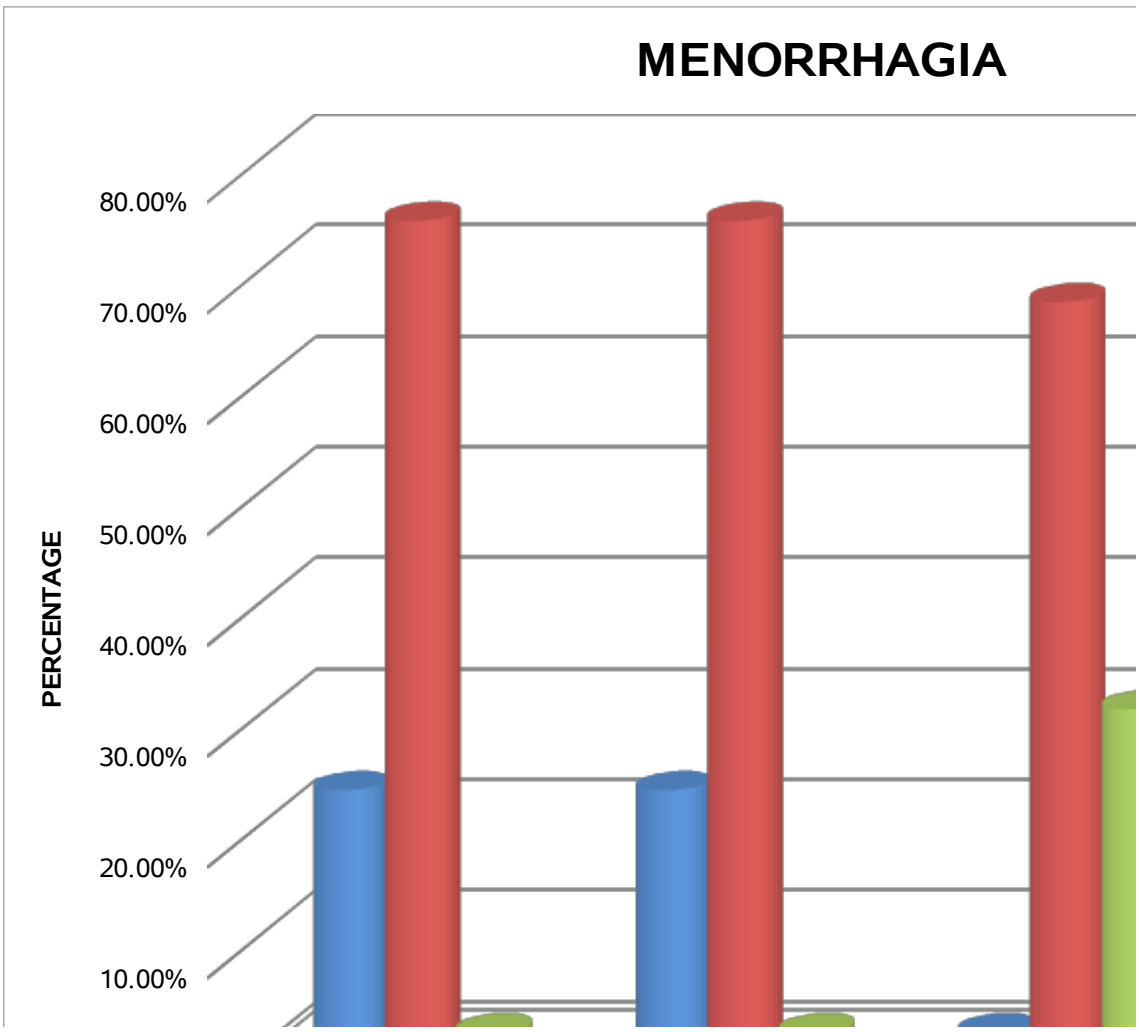

MENORRHAGIA
PERCENTAGE
80.00%
70.00%
60.00%
50.00%
40.00%
30.00%
20.00%
10.00%

TABLE-14

OLIGOMENORRHEA -T_3,T_4 AND TSH VALUES

Values	T3 (N=0.5-1.5 ng/ml)		T4 (N=4.8-11.5µg/dl)		TSH N=0.3-6.18µIU/ml)	

	No.of pts.	Percentage	No.of pts.	Percentage	No.of pts.	Percentage
< Normal	4	5.19%	4	5.19%	5	6.49%
Normal	70	90.90%	70	90.90%	67	87.01%
>Normal	3	3.90%	3	3.90%	5	6.49%

Out of 77 Oligomenorrheic patients,

4 patients(1.6%*) had clinical hypothyroidism
3 patients(1.2%*) had had clinical hyperthyroidism
1 patient(0.4%*) had subclinical hypothyroidism
2 patients(0.8%*) had subclinical hyperthyroidism in this group.

* → of the total sample studied

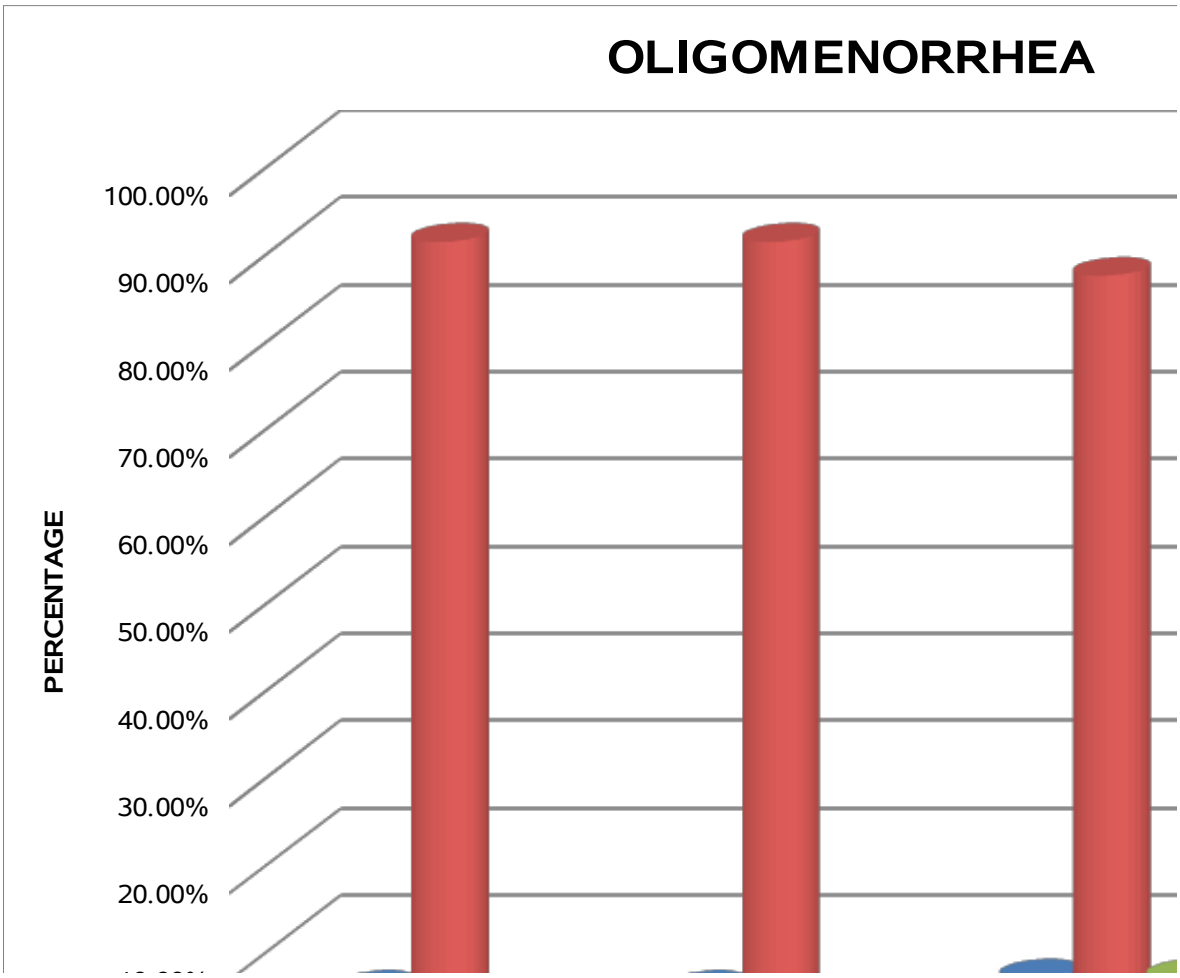

OLIGOMENORRHEA
PERCENTAGE
100.00%
90.00%
80.00%
70.00%
60.00%
50.00%
40.00%
30.00%
20.00%

TABLE-15

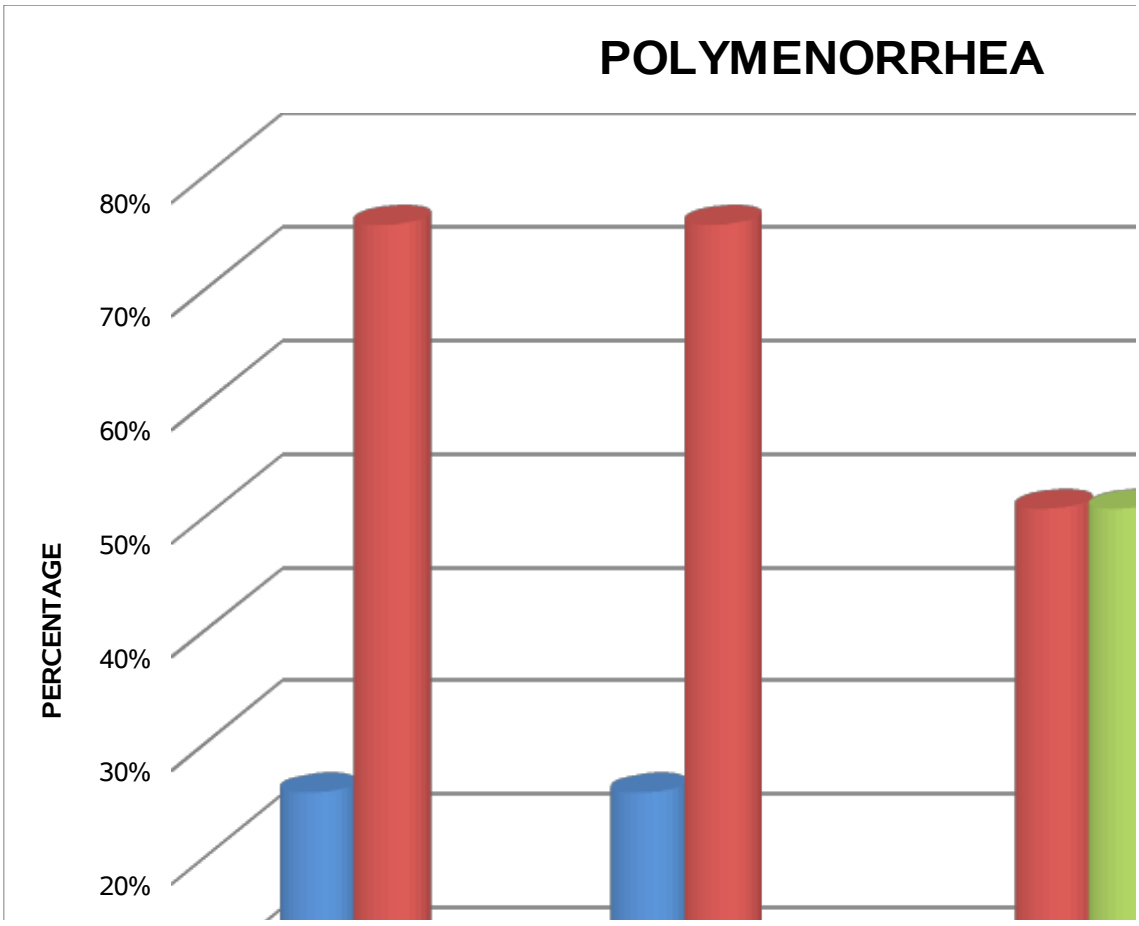
POLYMENORRHEA-T_3,T_4 AND TSH VALUES

Values	T3 (N=0.5-1.5 ng/ml)		T4 (N=4.8-11.5µg/dl)		TSH N=0.3-6.18µIU/ml)	

	No.of pts.	Percentage	No.of pts.	Percentage	No.of pts.	Percentage
< Normal	2	25%	2	25%	-	-
Normal	6	75%	6	75%	4	50%
>Normal	-	-	-	-	4	50%

Among 8 patients with polymenorrhea,
2patients(0.8%*) had clinical hypothyroidism
2patients(0.8%*) had subclinical hypothyroidism
No clinical and subclinical hyperthyroidism was noted in polymenorrhea patients.

*→ of the total sample studied



The Findings are summarized as follows:

TABLE-16

Incidence of	Based on T_3,T_4 and TSH
Hypothyroidism	13.6%
Hyperthyroidism	4%
Subclinical Hypothyroidism	4.8%
Subclinical Hyperthyroidism	1.6%

In this study,Thyroid dysfunction account for 24 % in AUB patients.

The incidence of thyroid Dysfunction in different types of AUB is as follows:

TABLE-17

AUB	Hypo thyroidism	Hyper thyroidism	Subclinical hypothyroidism	Subclinical hyperthyroidism
Amenorrhea	0.8%	2.4%	0.4%	0.8%
Menorrhagia	10.4%	0.4%	3.2%	-
Oligomenorrhea	1.6%	1.2%	0.4%	0.8%
Polymenorrhea	0.8%	-	0.8%	-

DISCUSSION

AUB is a benign yet debilitating disease with a strong association with thyroid disorders. Our study highlights the association between AUB and thyroid dysfunction by measurement of T_4 and TSH in the fasting state in women with AUB.

Hypothyroidism is observed in 10.4% of women with menorrhagia, and 0.8% of women with amenorrhea. Hyperthyroidism is seen in 1.2% of women with oligomenorrhea. The overall incidence of thyroid dysfunction is 24%. This correlates with the study by Wilansky et al, 1992.

Study	Incidence of thyroid disorders
Prentice at al, 1999	36%
Wilansky et al, 1992	22%
Present study	24%
Menon et al, 1995	26%

Some patients have a normal serum TSH despite low T_3 and T_4. This is explained by a downward resetting of the threshold for TSH inhibition TSH setpoint for a particular serum T_3, T_4 increases with age and is also altered by personal and familial character. TSH values tend to change more rapidly because the half life of TSH is much shorter than T_3 and T_4. This should be considered with regard to abnormal relationships between T_3, T_4 and TSH. There are some variations which should be given due consideration before interpreting the results.

1) T_4- Methodology, pregnancy

2) TSH – diurnal variation, pulsatile secretion

Alteration in the relationship between $T_4$and TSH can be caused by alternate thyroid stimulating hormones like TSH isoforms, chorionic gonadotrophins, and TSH receptor stimulating antibody. It can be caused by hormones and drugs like glucocorticoids, severe non-thyroidal illness, recent thyrotoxicosis and long standing hypothyroidism. The incidence of thyroid dysfunction in the population with AUB is 24% according to our study and hence selective screening of this population would result in a higher yield.

A major benefit of routine testing is the earlier detection of unsuspected overt thyrotoxicosis or subclinical hypothyroidism or hyperthyroidism. Most clinicians advocate treatment of women with elevated TSH levels in view of risk of hypothyroidism subsequently.

T_3 - Binding protein ,its values are altered in the following conditions like illness ,surgery, drugs and age related changes,

A T_3 T_4 TSH assay can be used as a management tool besides its use in diagnosis and screening A T3 : T4 eatio of greater than 0.024 during drug therapy suggests that remission is unlikely . it can be used to identify patients who have persistent T3 excess despite normal a low serum T4 levels during anti thyroid therapy. It can be used to distinguish between T3 thyrotoxicosis and subclinical thyrotoxicosis in patients with low TSH.

SUMMARY

The present study is a cross-sectional study of 250 women with abnormal uterine bleeding in the reproductive age group undertaken in a tertiary referral hospital over a period of 10 months. It was done to ascertain the correlation between thyroid dysfunction and AUB.

The history was elicited according to the proforma. Anthroprometric measurement were taken and a detailed examination was done. T_3, T_4 and TSH levels were evaluated in the fasting rate and the results interpreted.

1. The study showed a significant correlation (p = 0.004, significant) between increasing age and thyroid dysfunction.

2. The general examination showed a significant correlation (p=0.003) with thyroid dysfunction.

3. The Body Mass Index showed a significant correlation (p=0.006) with thyroid dysfunction.

4. The study showed a significant correlation (p=0.006) between Hemoglobin Estimation and thyroid dysfunction.

5. The Study showed a significant correlation between thyroid profile (T_3,T_4 and TSH) and AUB (p=0.003).

6. The study showed a significant correlation (p=0.002, Significant) between fractional curettage and hypothyroidism whereas in hyperthyroidism as the endometrial pattern is unpredictable, it was not significant.

CONCLUSION

It may be concluded from the present study that there is a significant association between thyroid disorders and AUB. The high incidence (24%)of thyroid disorders in women with AUB, particularly if the 5-10% of subclinical hypothyroidism is included, justifies the cost of screening in AUB population. The risk of progression to overt hypothyroidism (about 5% per year) in patients with subclinical disease also emphasize the need for screening in AUB population.

PROFORMA

Name Age

Address Parity

Sterilisation

H/O O/E

Menorrhagia ☐ General Condition

Oligomennorrhe ☐ Anemia

Amenorrhea ☐ Thyromegaly

Polymenorrhea ☐ BMI

Others ☐

H/O S/S Hyperthyroidism Thyroid function tests

T3

---------- T_4

---------- TSH

---------- Inference

H/O S/S Hypothyroidism other Investigation

---------- Hb in gm/dl

---------- Fractional Curettage

BIBLIOGRAPHY

1. Anasti JN, Flack MR, Froehlich, J, Nelson IM, Nisula BC. A Potential novel mechanism for precocious puberty in juvenile hypothyroidism, J. Clin. Endocrinol. Metab.80:276, 1995.
2. Balen AH, Shoham Z and Jacobs HS (1933a). Amenorrhea- causes and consequences In-Asch RH and studd JJW (eds) Annual progress in reproductive medicine. Carnforth, Lancashire: Pantheon press, pp- 205-34.
3. Ballabio, M.Poshyachinda M, Ekins RP, Pregnancy induced changes in thyroid function : role of human chorionic gonadotropin as putative regulator of maternal thyroid, J.Clin.Endocrinol. Metab. 73:824,1991.
4. Blum M. Blum G. The possible relationship between menorrhagia and occult hypothyroidism in IUD wearing women. Advance contracep. 1992:8:313-317.
5. Bolmet HG, Fieldler K Leindenberger FA. Subclinical hypothyroidism and infertility. Lancet. 1981;2:1278.
6. Bottazo GF. Dean BM. Autoimmune thyroid disease. Anuu Rev Med. 1986:37 353-354.
7. Boukis MA, Koutrar DA, Souvatzoglou A, et al. Thyroid hormone and immunological studies in an endemic goiter area. Arch klin med 1968, 215:270-284.

8. Brent GA, the molecular basis of thyroid hormone action, new Eng. J. Med 331-947.1994
9. Brenta G, Schnitman M, Gurfinkiel M, et al variations of sex hormone binding globulin in thyroid dysfunction. Thyroid 1999;9:273-277.
10. Burrow GN, Fisher DA, Larsen PR, Maternal and fetal thyroid function, New Engl. J. Med . 331:1072, 1994.
11. Caldwell G, Kellet KA, Gow SM et al . A new strategy for thyroid function testing. Lancet 1985:1:1117-1119.
12. Cameron IT (1992). Medical Management of menorrhagia .Curr obstet, Gynaecol 2,136-40
13. Contreras P, Generini G, Michelson H ,Pumarino H, Compmo, Hyperprolactinemia and galactorrhea: Spontaneous versus iatrogencic hypothyroidism, J.Clin Endocrinol. Metab 53:1036,1981
14. Cooper D, Ridgway E, Kilman B, et al Metabolic Clearance and production rates of prolactin in man, J. Clin Invest. 1979; 64:1669-1680.
15. Cooper DS, thyroid hormone treatment: New insights into an old therapy,JAMA 261:2694,1989.
16. Coulter A , Bradlow J, Agass M, Martin Bates C, Tulloch A. outcomes of referrals to gynaecology out patient clinics for menstrual problems: an audit of general practice records. Br. J. obstel Gynacecal 1991,98:789-796.

17. Danese Md, powe NR, Sarvin CT, Landenson PW, screening for mild thyroid failure at the periodic health examination. A decision and cost effective analysis JAMA 276:285, 1996.

18. Davey DA, Dysfunctional uterine bleeding In: Whitfield CR, ed Dewhursts textbook of obstetrics and gynaecology for postgraduates, 5th edn. London, Blackwell, scientific 1995, p 599.

19. Del . Pozo E, wyss H. Tolis G, et al , prolactin and deficient luteal function, obstet, Gynaecol. 1979; 53:282-286.

20. Doody KM and carr BR (1990). Amenorrhea: in : Chihal HJ, London SN (eds) Menstrual cycle disorders, obstet. Gynecol Clinical N.Am Philadelphia : Saunders, 17:361 87.

21. Drexhage HA, Bottazzo GF, Bitenusky L, et al. Thyroid growth blocking antibodies in primary myxedema. Nature 1981;239:594-595.

22. Edlend M,Magmusson C, Ven shoultz, B. Quality of life a swedish survey of 220 women. In smith SK, ed. Dysfunctional uterine bleeding London :Royal society of Medicine press, 1994; pp.36-37.

23. Ericson, GF. An analysis of follicle development and ovum maturation, seminars Reprod Endocrinol. 4:233,1986.

24. Falsetti L,Pasinetti E, Mazzani MD, Gastaldi A, weight loss and menstrual cycle clinical and endocrinology evaluation, gynecol enodcrinol , 6:49, 1992

25. Fraser IS. Treatment of menorrhagia In: Drife JO, Ed. Dysfunctional uterine bleeding and menorrhagia, bailliere's clinical obstertrics and gynaecology. London. Bailliere Tindal. 1989:pp.391-402
26. Gennazani Ar, petragtia F, De Ramundo BM, et al, Neuroendocrine correlates of stress related amenorrhea: Ann N.Y. Acad. Sci 1991;626:125-129.
27. Glinoer D, The regulation of Thyroid function in pregnancy: Pathways of endocrine adaptation from physiology to pathology, Endocr Rev.18:404,1997.
28. Glinoer, D, De Nayer P.Bourdoux P, Lemone M.Robyn C, Van Stirteghem A, Kinthaert, J, Clin . Endocrinol. Metab. 71:276, 1990.
29. Hague WM, Tan SL, Adams , J and Jacobs HS (1987) Hypergonadotrophic amenorrhea- etiology and outcome in 93 young women .Int.j.Gynacol. obstet, 25,121-5.
30. Haisen KA, Tho SPT, Hamly M, Moretizzo RW, Mc donough PG, Massive Ovarian Enlargement in primary Hypothyroidism , fertil steril 67:169,1997.
31. Herzog, DB, Copeland PM. Eating disorders N.Engl J. Med, 1985,313:295-303.
32. Hiller G(ed)(1991)ovarian endocrinology.oxford:Blackwell science.

33.Hingham JM, Shaw RW. The effect of thyroxine replacement on menstrual blood loss in a hypothyroid patient, Br.J.Obstet, Gynaecol, 1992:99:695-696.

34.Hirvonen E, Etiology, clinical features and prognosis in secondary amenorrhea, Int. J. Fertil. 22:69, 1977.

35.Hung W, August GP, Glasgow AM, Pediatric Endocrinology, medical Examination publishing Co., Garden City, 1978.

36. Kamilaris TC, De Bold LR, Pavlov SN, et al, Effect of altered thyroid hormone levels on Hypothalamic pituitary adrenal function . J. Cin Endocrinal Metab. 1987, 65:994-999.

37.Kellet KA, Van Herle AJ, Honbok, Serum prolactin untreated primary hypothyroidism AM. J. Med. 1978;64;782-787.

38.Keye WR, Ho Yuen B, Knopff R, et al Amenorrhea, hyperprolactinemia and pituitary enlargement secondary to primary hypothyroidism. Obset. Gynecol. 1976; 48:697-702.

39.Kimura M, Amino N. Tamaki H, Mitsuda N, Miyai K, Tamizawa O, physiologic Thyroid activation in normal early pregnancy is induced by circulating. hcG, obstet. Gyneocl . 75; 775,1990.

40.Koutras DA, Disturbances of menstruation in thyroid disease. Ann. N.Y. Acad. Sci. 1997:816:280-284.

41.Kramer, M Kaushansky A. Genel M. Adolescent secondary amenorrhea: association with hypothalamic hypothyroidism , paediatrics 1979;94:300-303.

42.La Barbera A, Miller MM, Ober C, et al., Auto immune etiology in premature ovarian failure. Am. J. Reprod. Immuno.1988; 16:114-118.

43.Lazarus JH, Hyperthyroidism , Lancet 349:339,1997.

44. Lee PA, Van Dop C, Migeon CJ, Mc Cune Albright syndrome long term follow up JAMA 256:290,1986.

45. Leon speroff, Robert H.Glas Nathan, G.Kase Clinical gynaecologic endocrinology and infertility sixth edition, 1999.

46.Mackenzie JM, Zakariya M. Hyperthyroidism in Degroot LJ, Cahill GF, Martini L, eds. Endocrinology , New York :Greene and Stratton 1979:647.

47.Medvei, VC. The history of clinical Endocrinology. The pantheon publishing group, New York, 1993.

48.Mindermann T, wibon CB, Thyrotropin Producing pituitary Adenomas, J Neurosurg 79:521,1993.

49. Munster K, Schmidt I, Helm P. Length and Variation in the menstrual cycle- a cross sectional study from a Danish country, Br. J. Obstet, Gynaccol. 99:422, 1992.

50.Natori, S. Karashima, T, Koga S.et al :Effect of thyroid hormone replacement on reduction of pituitary enlargement and restoration of fertility- fukuoka Igaku Zasshi 1991;82;461-463

51.Nelson L. Rybo G, Treatment of menorrhagia. Am. J. Obstet. Gynecol. 110:713, 1971

52.Norman AW, Litwack G. Thyroid Hormones. In: Norman AW Litwack G, eds. Hormones, San Diego, Academic press , 1987;221.

53.Olson BR. Exercise induced amenorrhea. Am. Fam. Physician 1989, 39:213-221.

54.Peterson CM. Thyroid disease and fertility In: Gleichon N, ed. Autoimmunity in reproduction. Immunol. Allergy clin. NA. 1995; 14:725-738.

55.Poretsky L, Garber J, Kleefield J, Primary amenorrhea and pseudo prolactinoma in a patient with primary hypothyroidism. Am J Med 81:180, 1986.

56.Rebar RW, Kenisberg D, Hodgen GD. The normal menstrual cycle and the control of ovulation, In :Becker KL, Ed. Principles and practice of endocrinology and metabolism. 2nd ed. Philadelphia. JB lippincott 1995:868.880

57. Reindollar RH, Novak M, Tho SPT,Mc Donough PG, Adult onset amenorrhea, AM J Obstet Gynecol 155:531,1986.

58. Reindollar RH, Tho SPT, Mc Donough PG, Delayed Puberty: an updated study of 326 patients, Trans Am. Gynecol. Obstetric. Soc. 8:146,1989.

59. Royal college of General Practitioners and the office of population surveys morbidity statistics from general practice 1981-2 London HMSO, 1986.

60. Scanlon MF, Chass V, Health M, et al, Dopaminergic content of thyrotropin α and β subunit, and prolactin in euthyroidism and hypothyroidism J. Clin. Endocrinol. Metab 1981; 53; 360-365.

61. Scott JC,Mussy E menstrual patterns of myxedema.Am.J.Obstet.Gynaecol.1964;90:161-165

62. Smyth PPA, Hetherton AMT, Smith DF, Radcliff M, O' Herlihy C, Maternal Iodine status and thyroid volume during pregnancy correlation with neonatal iodine intake, J. Clin Endocrinol. Metab 82: 2840, 1997.

63. Surks MI, Chopra IJ, Mariash CN, NiColoff JT, Solomon DH American Thyroid Association guidelines for use of laboratory tests in thyroid disorders JAMA 263:1529.1990

64. Tanaka, T, Tamai H, Kuma K, et al. Gonadotrophins response to LHRH in hyperthyroid patients with menstrual disturbances. Metabolism 1981; 30:323-325.

65. Thomas R, Reid RL. Thyroid disease and reproductive dysfunction Obstet. Gynaecol.1987;70:789-798.

66. Thomas R, Reid RL. Thyroid disease and reproductive function Obstet. Gynaecol.1987;70:789-798.

67. Treloar A E,Boynton RE, Borghilid GB,Brown BW.Variation of the human menstrual cycle through reproductive life,Int.J.Fertil.12:77,1967.
68. VanHearle AJ,Uller RP,Mathews ML et al Radioimmunoassay for measurement of Thyroglobulin in human serum.J.Clin Invest.1973;52;1320-1327.
69. Vander pump MPJ Turnbridge VMG.The thyroid fundamental and clinical text,7th edition.1996;474-482.
70. Vollman RP,The menstrual cycle,In:Friedman,ed.Major problems in obstetrics and gynaecology,W.B.SaundersCo.,Philadelphia,1977.
71. Warfel W.Thyroid regulation pathways and its effect on human function 1992;32:145-150.
72. Wilansky DL,Greisman B,Early hypothyroidism in patients with menorrhagia. *Am.J.Obstet.Gyneacol* 160;673:1989.
73. Wilkins L. The diagnosis and treatment of Endocrine disorders in childhood and adolescence,3rd ed.,Charles C,Thomas,Spring Field,1965 Thomas R, Reid RL. Thyroid disease and reproductive dysfunction obster. Gynecol 1987;70:789-798.
74. Thomas R, Reid RL. Thyroid disease and reproductive function. Obstet Gynecol .1987:70;787-798.

ABBREVIATIONS

AUB	-	Abnormal Uterine Bleeding
T_4	-	Thyroxine
T_3	-	Tri-iodothyronine
TSH	-	Thyroid Stimulating Hormone
TRH	-	Thyrotropin Releasing Hormone
LH	-	Luteinising Hormone
FSH	-	Follicular Stimulating Hormone
HCG	-	Human Chorionic Hormone
TR	-	Thyroid hormone Receptor
RXR	-	Retinoid X Receptor
RT_3	-	Reverse T_3
TBG	-	Thyroid Binding Globulin
SHBG	-	Sex Hormone Binding Globulin
FT_4	-	Free Thyroxine
TT_4	-	Total Thyroxine
GnRH	-	Gonadotrophin Releasing Hormone
Anti TPO	-	Anti Thyroid Peroxidase
Anti TG	-	Anti Thyroglobulin
BMI	-	Body Mass Index
PID	-	Pelvic Inflammatory Disease
IUCD	-	Intra Uterine Contraceptive Device
IRMA	-	Immuno Radio Metric Assay
BRIT	-	Board of Radiation and Isotope Technology
ACOG	-	American College of Obstetric and Gynaecology